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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/933,640	08/20/2001	Eliezer Masliah	6627-PA1071	6686

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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/933,640	MASLIAH ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *37 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36,38 and 40-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/9/02 & 5/8/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response filed May 8, 2006 has been entered.

Applicants' election without traverse of Group I, Claims 1-36, 38, and 40-42 in the response filed May 8, 2006 is acknowledged. The elected invention is drawn to a transgenic mouse comprising, integrated into its genome, a gene encoding human amyloid precursor protein and a gene encoding human α-synuclein.

The restriction requirement is still deemed proper and is therefore made FINAL.

It is noted that Claims 1-3, 11, and 15-17 encompass non-elected subject matter. Thus, Claims 1-3, 11, and 15-17 are examined herein only to the extent that they encompass the elected subject matter.

Claims 1-22 remain pending in the instant application.

Claims 37 and 39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. The election was made without traverse in the response filed May 8, 2006.

Accordingly, Claims 1-36, 38, and 40-42 are examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-36, 38, and 40-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising: a first transgenic nucleotide sequence, integrated into the genome of said mouse, comprising a sequence encoding the wild-type

human amyloid precursor protein, 751 amino acid isoform (hAPP751), operably linked to a neuron-specific promoter; and a second transgenic nucleotide sequence, integrated into the genome of said mouse, comprising a sequence encoding wild-type human α-synuclein operably linked to a neuron-specific promoter; wherein the first and second transgenic nucleotide sequences are expressed, and wherein said transgenic mouse develops amyloidosis, neurofibrillary tangles, and intraneuronal accumulation of α-synuclein,

does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants are reminded that the above-indicated scope of enablement is not meant to suggest specific claim language and that proper support in the as-filed specification for any claim terminology introduced by amendment is always required.

The specification fails to provide an enabling disclosure for the preparation of the full scope of genetically-modified mice as claimed exhibiting an appropriate phenotype, other than the transgenic mice as set forth above, because the phenotype of a transgenic mouse cannot be predicted.

The specification fails to provide an enabling disclosure for the full scope of the claimed transgenic mice because the claims cover mice having a variety of different phenotypes. The mere capability to perform gene transfer in any given species is not enabling for the claimed transgenic mice and methods of producing them because the desired phenotype cannot be predictably achieved by simply introducing a construct as recited in the claims. While gene transfer techniques are well-developed for a variety of species, methods for achieving the desired level of transgene expression in appropriate tissues are less well-established. With regard to transgenic animals, the introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene

transfer typically relies on random integration of the transgene construct or no integration. When random integration occurs, insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant genetically-modified animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic mouse depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, a construct that confers the desired phenotype in a rat cannot necessarily achieve the same result in a mouse. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). Even differences in the genetic background of transgenic mice can have an unpredictable effect on phenotype (Sigmund, 2000). In the absence of specific guidance, the production of a transgene-dependent phenotypic alteration resulting from the introduction of a nucleic acid construct as recited in the claims, is unpredictable. Thus, given the limited working examples directed exclusively to transgenic mice of the phenotype noted about, the existence of any phenotypic alteration resulting from the introduction of other transgenes as recited in the claims, is highly unpredictable. Given the limited working examples and the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue experimentation in order to make and use the claimed transgenic mice over the full scope.

Houdebine (1994) discloses that in the field of transgenics, constructs must be designed case by case, without general rules, to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (page 275, column 1, paragraph 1). Wall (1996) discloses the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements, and may result in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Additionally,

Kappel et al. (1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, paragraph 4). The level of skill in the art of *in vivo* genetic modification is such that one cannot predict whether a transgene that is expressed in a mouse will also be expressed efficiently in another animal. For example, Strojek and Wagner (1988) point out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, including pigs and rabbits, because, for example, the cis-acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 238-239). Furthermore, Wall (1996) explicitly teaches that transgene expression and the physiological consequences of transgene expression are not always accurately predicted in transgenic mouse studies (page 62, paragraph 1).

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into a mouse, specific guidance must be provided to enable the instant invention over the full scope. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The claims cover the use of the transgenic mice as a model for Alzheimer's Disease, but the specification does not enable this use for any phenotype other than those indicated above. In the absence of specific guidance for making and using transgenic mice exhibiting an appropriate phenotype, undue experimentation would have been required to make and use the full scope of the claimed mice and practice the claimed methods over the full scope.

Accordingly, given the demonstrated lack of predictability in the art, the limited amount of direction given, the state of the prior art, the quantity of experimentation needed, and the limited applicable working examples, one of skill in the art would not be able to make and use the claimed invention over the full scope without undue experimentation.

Conclusion

No claims are allowable.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER